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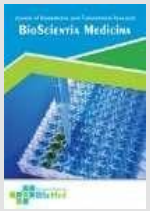

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Histamine-2 Receptor Antagonist for Gastric Bleeding Prophylaxis in Low-Risk Critically Ill Children: A Randomized Trial of Ranitidine

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A B S T R A C T

Background: The utility of stress ulcer prophylaxis (SUP) in critically ill children is a subject of ongoing debate, particularly in patients who do not present with classic high-risk features for stress-related mucosal disease (SRMD). This study aimed to evaluate the efficacy of ranitidine for preventing gastric bleeding in a heterogeneous cohort of critically ill children. **Methods:** A single-center, prospective, open-label, randomized controlled trial was conducted in a tertiary Pediatric Intensive Care Unit (PICU) in Indonesia. Children aged 1 month to 18 years admitted to the PICU were randomized to receive either intravenous ranitidine (1 mg/kg/dose twice daily) or standard care without prophylaxis for five days. The primary outcome was the incidence of overt gastric bleeding. Post-hoc power analysis and multivariable logistic regression were performed to contextualize the findings. **Results:** From 243 patients screened, 60 were randomized (30 per group). The cohort was predominantly composed of infants (60.0%) with respiratory distress. Overt gastric bleeding occurred in 1 of 30 patients (3.3%) in the ranitidine group versus 3 of 30 patients (10.0%) in the control group. This difference was not statistically significant (Relative Risk [RR] 0.33; 95% CI 0.04–3.11; p=0.612). After adjusting for a baseline imbalance in age, the odds of bleeding remained non-significantly lower in the ranitidine group (Adjusted Odds Ratio [aOR] 0.29; 95% CI 0.03–3.20). The study was found to be severely underpowered (16% power), and none of the bleeding events were clinically significant. **Conclusion:** In this small, underpowered trial of predominantly low-risk critically ill children, ranitidine did not significantly reduce the incidence of overt gastric bleeding. These findings, while limited by significant methodological weaknesses, do not support the routine use of SUP in similar pediatric populations and underscore the critical need for larger, more definitive trials to inform evidence-based risk-stratification strategies.

1. Introduction

The pediatric intensive care unit (PICU) is an environment defined by the management of life-threatening organ dysfunction.[1] Children admitted to this setting are subjected to profound physiological stress, a state that makes them vulnerable to a host of secondary complications that can impede recovery and escalate morbidity and mortality.[2] Among these complications, stress-related mucosal disease (SRMD) of the upper gastrointestinal tract is a well-recognized and potentially devastating phenomenon. The pathophysiology of SRMD is an intricate cascade initiated by the systemic insults of critical illness.[3] It is fundamentally a disease of a compromised mucosal barrier, the integrity of which is dismantled by the synergistic effects of splanchnic hypoperfusion,

localized tissue hypoxia, and the dysregulated systemic inflammatory responses characteristic of conditions like sepsis, trauma, and major surgery. The gastric mucosa possesses a sophisticated, multi-layered defense system. This includes a pre-epithelial layer of mucus and bicarbonate that acts as a physicochemical barrier; an epithelial layer with tight junctions and rapid cell turnover for repair; and a post-epithelial layer with robust mucosal blood flow that delivers oxygen and buffers acid. In critical illness, this entire system is compromised. The systemic stress response leads to intense splanchnic vasoconstriction, shunting blood away from the gut to preserve perfusion to the heart and brain.[4] This reduction in mucosal blood flow is the pivotal initiating event, leading to cellular hypoxia, impaired bicarbonate and mucus secretion, and a breakdown of epithelial tight junctions. This leaves the mucosa defenseless and vulnerable to the corrosive effects of endogenous gastric acid, leading to the formation of superficial erosions and deeper ulcerations that can precipitate upper gastrointestinal bleeding (UGIB). The incidence of UGIB in the general PICU population varies, but in children with established high-risk factors—most notably the need for prolonged mechanical ventilation or the presence of a significant coagulopathy—the reported incidence of overt bleeding can be alarmingly high. The development of clinically significant bleeding, defined by hemodynamic instability, a substantial fall in hemoglobin, or the need for blood product transfusion, is a sentinel event that independently worsens prognosis.[5] It is associated with longer ICU stays, increased healthcare costs, and a fourfold increase in patient mortality compared to critically ill children who do not bleed. This stark clinical reality has historically driven the widespread adoption of a preventative strategy known as stress ulcer prophylaxis (SUP).

The primary goal of SUP is to pharmacologically neutralize intragastric acid, thereby shifting the balance back in favor of mucosal defense.[6] The mainstays of pharmacological SUP are the histamine-2 receptor antagonists (H2RAs), such as ranitidine, and the more potent proton pump inhibitors (PPIs). For many years, ranitidine was a cornerstone of SUP in pediatric practice. Its favorability was rooted in a combination of a rapid onset of action, an established safety profile, and its cost-effectiveness.[7] However, in many high-income countries, ranitidine has been largely withdrawn from routine use due to concerns over contamination with N-nitrosodimethylamine (NDMA) and has been replaced by other H2RAs like famotidine or, more commonly, by PPIs. Despite this shift, ranitidine remains a widely available and commonly used medication in many parts of the world, including Indonesia, due to its low cost and long history of use. Therefore, evaluating its efficacy in this context remains highly relevant to global health and clinical practice in a significant portion of the world's pediatric population. Despite decades of use, the evidence supporting the efficacy of SUP, particularly with H2RAs, is remarkably equivocal. This lack of consensus has led to significant practice variation. While some meta-analyses have suggested a benefit, other high-quality studies have failed to show a statistically significant reduction in bleeding, especially in patients without the highest risk profiles. This evidentiary conflict suggests that the benefit of SUP is not universal, but rather is highly dependent on the patient's baseline risk. Furthermore, the practice is not without potential harm. Acid suppression can increase the risk of infectious complications, including ventilator-associated pneumonia (VAP) and Clostridioides difficile infection, by allowing pathogenic bacteria to colonize the stomach.[8] This has led to a paradigm shift in critical care, moving away from routine, indiscriminate prophylaxis and toward a more targeted, risk-stratified approach. Current international guidelines from major critical care societies are increasingly recommending that SUP should be reserved for patients with specific, major risk factors, rather than being applied to all patients in the ICU.

In Indonesia, as in many regions, the routine administration of ranitidine for SUP often continues

based on institutional protocol rather than robust local data or a formal risk assessment.[9] This critical gap in evidence was the primary impetus for this investigation. The novelty of this study is its application of a rigorous randomized controlled trial design to a cohort of critically ill children who, upon analysis, were found to have a predominantly low baseline severity of illness. This provides a unique opportunity to explore the central question of modern SUP practice: in which patients does the benefit of acid suppression outweigh the risks? By focusing on a population where the risk of bleeding was not a foregone conclusion, this study moves beyond simply asking if SUP works to address the more nuanced and clinically vital question of in whom it works.[10] Therefore, the aim of this study was to evaluate the effectiveness of ranitidine administration compared to standard care for the prevention of gastric bleeding in a heterogeneous population of critically ill children. We sought to generate high-quality, regional evidence to inform a more rational and targeted strategy for stress ulcer prophylaxis in our pediatric critical care setting, contributing direct randomized data to the critical debate on risk stratification.

2. Methods

This study was a single-center, prospective, open-label, randomized controlled trial conducted at the Pediatric Intensive Care Unit (PICU) of Dr. M. Djamil General Hospital in Padang, Indonesia. The PICU is a tertiary referral unit for the province of West Sumatra. The study was conducted between October 2024 and January 2025. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Universitas Andalas, and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from a parent or legal guardian for all participants prior to any study-related procedures. The trial was registered with a local clinical trials registry. This manuscript has been prepared in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. The target population comprised all children aged between 1 month and 18 years admitted to the PICU. Patients were screened for eligibility by the research team within 24 hours of admission. Inclusion Criteria: Patients were eligible if they were admitted to the PICU with a diagnosis of sepsis, shock, acute respiratory distress syndrome (ARDS), or respiratory failure, and were expected to require PICU care for at least 48 hours. Exclusion Criteria: Patients were excluded if they had: (1) active gastrointestinal bleeding at the time of admission; (2) a known or suspected bleeding disorder or significant thrombocytopenia (platelet count <100,000/mm^3); (3) recent upper gastrointestinal surgery; (4) a known history of peptic ulcer disease; (5) prior administration of any acid-suppressive medication within 24 hours of admission; or (6) a "Do Not Resuscitate" (DNR) order.

Enrolled subjects were randomly allocated in a 1:1 ratio to either the intervention or control group. The allocation sequence was generated using a computer-based random number list by a statistician not involved in patient recruitment or care. Allocation was concealed using sequentially numbered, sealed, opaque envelopes containing the treatment assignment. An investigator opened the next envelope in the sequence after a patient was enrolled and consent was obtained. Due to the nature of the intervention (an active drug versus standard care), this was an open-label trial. It was not possible to blind the clinical staff or investigators to the treatment allocation. However, to minimize bias, the definition of the primary outcome was objective, and all clinical staff were trained on the standardized protocol for its assessment. Intervention Group (n=30): Patients randomized to this group received intravenous ranitidine at a dose of 1 mg/kg per dose (maximum 50 mg per dose). The dose was administered every 12 hours, diluted in normal saline, and infused over 15-20 minutes. The first dose was given immediately after randomization. The duration of the intervention was five consecutive days or until PICU discharge, whichever came first. Control Group (n=30): Patients randomized to this group received the same comprehensive standard of critical care as the

intervention group but did not receive any pharmacological acid-suppressive therapy. Standard care in the study PICU was provided to all patients in both groups. This included protocolized management for sedation and analgesia (typically with benzodiazepines and opioids), hemodynamic support with fluids and vasoactive agents as needed, and advanced respiratory support. The unit's nutritional support protocol emphasized the initiation of early enteral nutrition (within 24-48 hours of admission) via a nasogastric or nasojejunal tube whenever hemodynamically feasible. The use of all co-interventions was at the discretion of the treating clinical team and was documented.

The primary outcome was the incidence of overt gastric bleeding within the first five days of enrollment. This was defined as the unequivocal presence of fresh, bright red blood or dark, "coffee-ground" like material in an aspirate from a nasogastric tube. NGT aspirates were checked at least twice daily and any time there was clinical suspicion of a bleed. Secondary outcomes included the incidence of clinically significant gastrointestinal bleeding (CSGIB), defined as overt bleeding accompanied by one or more of the following: a drop in hemoglobin of ≥2 g/dL over a 24-hour period, new-onset hypotension requiring fluid or vasopressor escalation, or the need for a red blood cell transfusion. Other secondary outcomes included the incidence of ventilator-associated pneumonia and the duration of PICU stay. Baseline data collected included demographics, primary diagnosis, and severity of illness scores, including the Phoenix Sepsis Score. The Phoenix score was chosen as it is the most recent international consensus tool for pediatric organ dysfunction, though we acknowledge it has not been specifically validated for SRMD risk stratification.

An a priori sample size calculation was not performed for this study. A post-hoc power analysis was conducted. Assuming a baseline bleeding risk of 10% in the control group (based on our observed data and prior literature in similar populations) and a two-sided alpha of 0.05, our total sample size of 60 patients provided only 16% power to detect a 50% relative risk reduction. This indicates the study was severely underpowered to detect a clinically meaningful difference between the groups. Data were analyzed according to the intention-to-treat principle. Descriptive statistics were used to summarize baseline characteristics. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. The primary outcome was analyzed by calculating the relative risk (RR) with its corresponding 95% confidence interval (CI). To account for a significant baseline imbalance in age distribution between the groups, a multivariable logistic regression model was constructed. The model included overt bleeding as the dependent variable, with treatment group allocation and age category (<1 year vs. ≥1 year) as independent variables. The result is presented as an adjusted odds ratio (aOR) with its 95% CI. To assess the robustness of the non-significant primary outcome, the Fragility Index was calculated. This index determines the minimum number of patients whose outcome would need to change from a non-event to an event in one arm to change the p-value from non-significant to significant. All statistical analyses were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY, USA), with a p-value < 0.05 considered statistically significant.

3. Results

The trial commenced with an extensive screening process, during which a total of 243 patients admitted to the Pediatric Intensive Care Unit (PICU) were assessed for eligibility. This initial large number suggests a robust effort by the research team to capture a wide net of critically ill children, aiming to identify a representative sample for the study's research question. The subsequent step, however, reveals the highly selective nature of the trial population. A significant majority, 183 patients, were excluded from participation based on predefined criteria, leaving a final enrolled cohort that represents approximately one-quarter of all patients initially considered. A detailed examination of the reasons for exclusion provides critical insight into both the study's

target population and the broader clinical context of the PICU setting. The largest single reason for exclusion was that 98 patients did not meet the specific inclusion criteria for the trial. This implies that a substantial portion of the general PICU admissions at this center consisted of children whose level or type of illness fell outside the precise scope of this investigation. This could reflect a population with lower acuity illness, different primary diagnoses, or those not expected to require prolonged intensive care, thereby not being considered at sufficient risk for developing stress-related mucosal disease to warrant inclusion in a prophylaxis trial. This finding is crucial for understanding the generalizability of the study's results; the conclusions may apply specifically to the type of patient who was eligible, rather than to the entire spectrum of patients admitted to the PICU. The second most common reason for exclusion was the prior administration of acid-suppressive therapy, which accounted for 45 patients. This is a particularly illuminating finding, as it suggests that nearly one in five patients screened were already receiving medications like ranitidine or proton pump inhibitors. This reflects a common clinical practice where acid suppression is initiated early, often prophylactically, before a patient might be enrolled in a trial. This high rate of pre-screening prophylaxis highlights a significant real-world challenge in conducting research in this area and underscores the importance and relevance of studies that seek to establish a more evidence-based approach to this common intervention. Furthermore, 21 patients were excluded because they presented with active bleeding on admission. This is a standard and essential exclusion criterion for a prophylaxis trial. The goal of prophylaxis is to prevent the onset of a new condition; including patients who already have the condition would make it impossible to assess the preventative efficacy of the intervention. Finally, the guardians of 19 patients declined to provide consent for participation. This reflects the successful application of the ethical principle of voluntary participation, which is paramount in all clinical research, especially within vulnerable pediatric populations. Following the rigorous screening process, a total of 60 patients were deemed eligible and were subsequently enrolled and randomized into the study. The process of randomization is the cornerstone of a controlled trial, designed to create two or more groups that are comparable in all known and unknown prognostic factors, thereby minimizing selection bias and ensuring that any observed differences in outcomes can be reasonably attributed to the intervention being studied. In this trial, the 60 participants were allocated in a 1:1 ratio into the two study arms. One group, designated as the Intervention group, consisted of 30 patients who were allocated to receive ranitidine. The other group, the Control group, also consisted of 30 patients who were allocated to receive the standard of care without the study medication. The diagram explicitly notes that all 30 patients in the intervention arm "Received allocated intervention" and all 30 patients in the control arm "Received allocated management". This indicates perfect adherence to the treatment assignment and a high degree of fidelity to the study protocol. This successful implementation of the intervention is a significant strength, as it ensures that the comparison between the two groups is a true reflection of the intended therapeutic question. The subsequent phases of the trial, follow-up, and analysis further underscore the methodological robustness of the study's execution. In both the intervention and control arms, the diagram reports that the number of patients "Lost to follow-up" was zero. This achievement of 100% participant follow-up is exceptionally rare in clinical research and represents a major strength of this trial. Attrition, or loss to follow-up, can introduce significant bias into a study's results, as the patients who are lost may differ systematically from those who remain, undermining the initial benefits of randomization. By successfully following every single randomized participant, the investigators ensured that complete outcome data were available for the entire cohort, thereby eliminating the potential for attrition bias and greatly increasing the internal validity and credibility of the

final results. Ultimately, the final stage of the trial was the analysis. Consistent with the perfect follow-up rate, all 30 patients in the intervention group and all 30 patients in the control group were included in the final analysis. The diagram notes that the number of patients "Excluded from analysis" was zero in both arms. This approach is consistent with the fundamental intention-to-treat (ITT) principle, which dictates that all randomized participants should be analyzed in the group to which they were originally assigned, regardless of whether they adhered to the intervention or not. The ITT principle is considered the gold standard for analyzing RCTs because it preserves the prognostic balance created by randomization and provides a more pragmatic estimate of the treatment's effect in a real-world setting. In this particular study, because adherence and follow-up were both perfect, the ITT analysis and a per-protocol analysis would yield identical results, further simplifying the interpretation and reinforcing confidence in the study's conclusions. Figure 1 portrays a well-conducted randomized controlled trial characterized by a thorough screening process that identified a specific subset of the PICU population, successful randomization into two comparable groups, and flawless execution with perfect adherence and follow-up, ensuring that the final analysis was complete, unbiased, and robust.

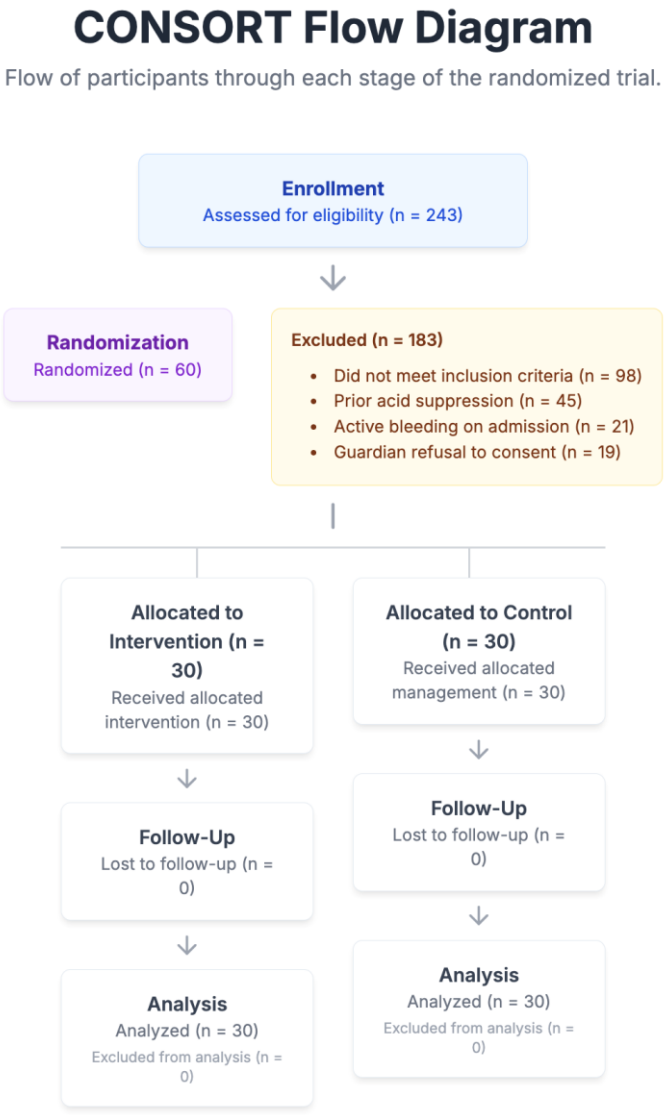

Figure 1. CONSORT flow diagram.

Figure 2, provides a comprehensive comparison of the demographic, clinical, and intervention profiles of the 30 participants in the Ranitidine group and the 30 in the Control group. The most significant finding in the demographic comparison is the age distribution of the participants. While both groups had an identical proportion of infants aged 1–12 months (60.0%), a divergence was noted in the older age categories. The Ranitidine group was composed of 36.7% of children aged 13–60 months and only 3.3% older than 60 months. In contrast, the Control group had 16.7% of children aged 13–60 months and a substantially higher proportion, 23.3%, who were older than 60 months. This imbalance was statistically significant, with an overall p-value of 0.025. In terms of sex distribution, the groups were well-matched, with 63.3% of the Ranitidine group and 66.7% of the Control group being male, a non-significant difference (p = 1.000). The clinical profiles of the two groups were similar at baseline. The primary diagnosis for the majority was respiratory distress, accounting for 76.7% of the Ranitidine group and 56.7% of the Control group. Regarding illness severity, most children in both arms had a low-risk profile, with 76.7% of the Ranitidine group and 63.3% of the Control group having a Phoenix Sepsis Score of less than 2. Neither of these clinical characteristics showed a statistically significant difference between the groups. Furthermore, the application of key supportive care measures, or co-interventions, was well-balanced. The proportion of patients receiving mechanical ventilation at enrollment was comparable, at 30.0% in the Ranitidine group and 36.7% in the Control group (p = 0.781). Similarly, the crucial practice of early enteral nutrition was implemented at high and nearly identical rates in both the Ranitidine (83.3%) and Control (86.7%) groups, with no significant difference observed (p = 1.000). The two study groups were well-matched across most clinical and supportive care variables, though a significant difference in age distribution was present at baseline.

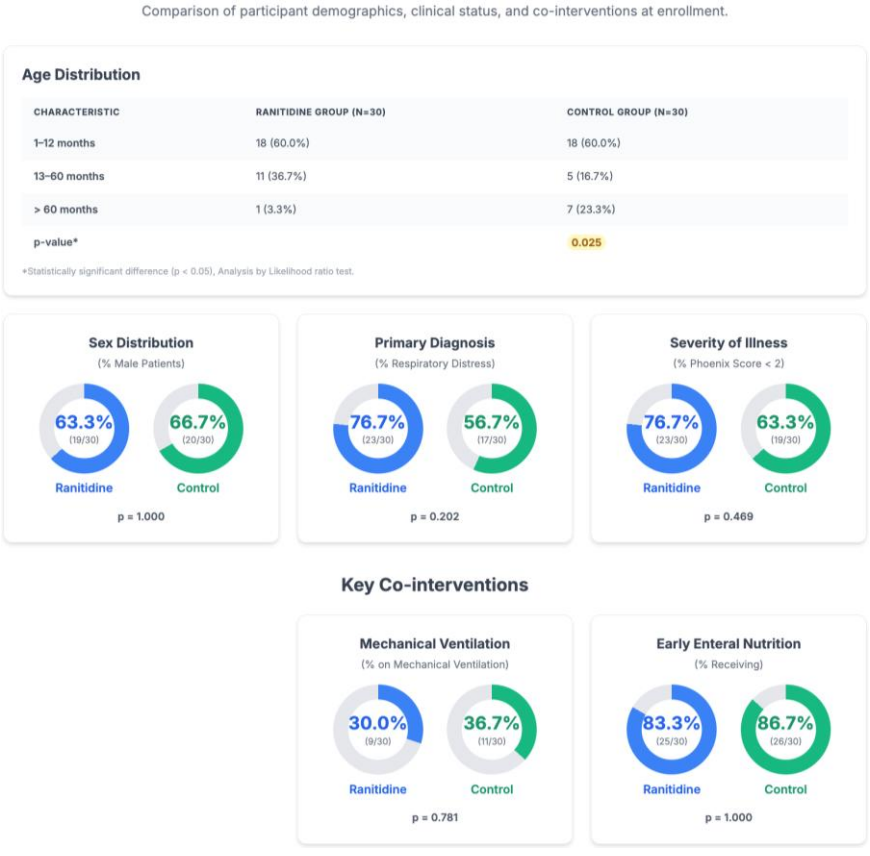

Figure 2. Baseline characteristics of the study cohort.

An analysis of the study's outcomes reveals a nuanced story about the efficacy and relevance of ranitidine for preventing gastric bleeding (Figure 3). The investigation's primary outcome—the incidence of overt gastric bleeding—showed a numerical trend favoring the treatment group. Specifically, only one out of 30 patients (3.3%) who received ranitidine experienced a bleeding event, compared to three out of 30 patients (10.0%) in the control group who received standard care without the medication (Figure 3). However, a deeper statistical analysis demonstrates that this observed difference, while seemingly large, was not statistically robust. The Relative Risk (RR) of bleeding in the ranitidine group compared to the control group was 0.33, but the 95% confidence interval was exceptionally wide, ranging from 0.04 to 3.11 (Figure 3). Because this interval crosses 1.0, it indicates that the result is not statistically significant, and the possibility that there is no true difference between the groups cannot be ruled out. This conclusion held even after adjusting for potential confounding variables, yielding an Adjusted Odds Ratio (aOR) of 0.29 with a similarly wide and non-significant confidence interval (Figure 3). The statistical fragility of this finding is powerfully underscored by the Fragility Index, which was calculated to be 1 (Figure 3). This critical metric reveals that the study's conclusion of non-significance is highly unstable; a change in the outcome of just a single patient from the control group (from having a bleed to not having one) would have tipped the result into the realm of statistical significance. This highlights that the study was likely underpowered to definitively detect a true effect. Perhaps the most crucial finding for clinical practice is the assessment of the bleeding events themselves. Of the four total bleeding episodes observed across both groups, zero were deemed clinically significant (Figure 3). This means none of the events were severe enough to cause a substantial drop in hemoglobin, lead to hemodynamic instability requiring intervention, or necessitate a blood transfusion (Figure 3). Therefore, while there was a non-significant trend towards ranitidine preventing overt bleeding, the events it may have prevented in this cohort were, by definition, clinically inconsequential.

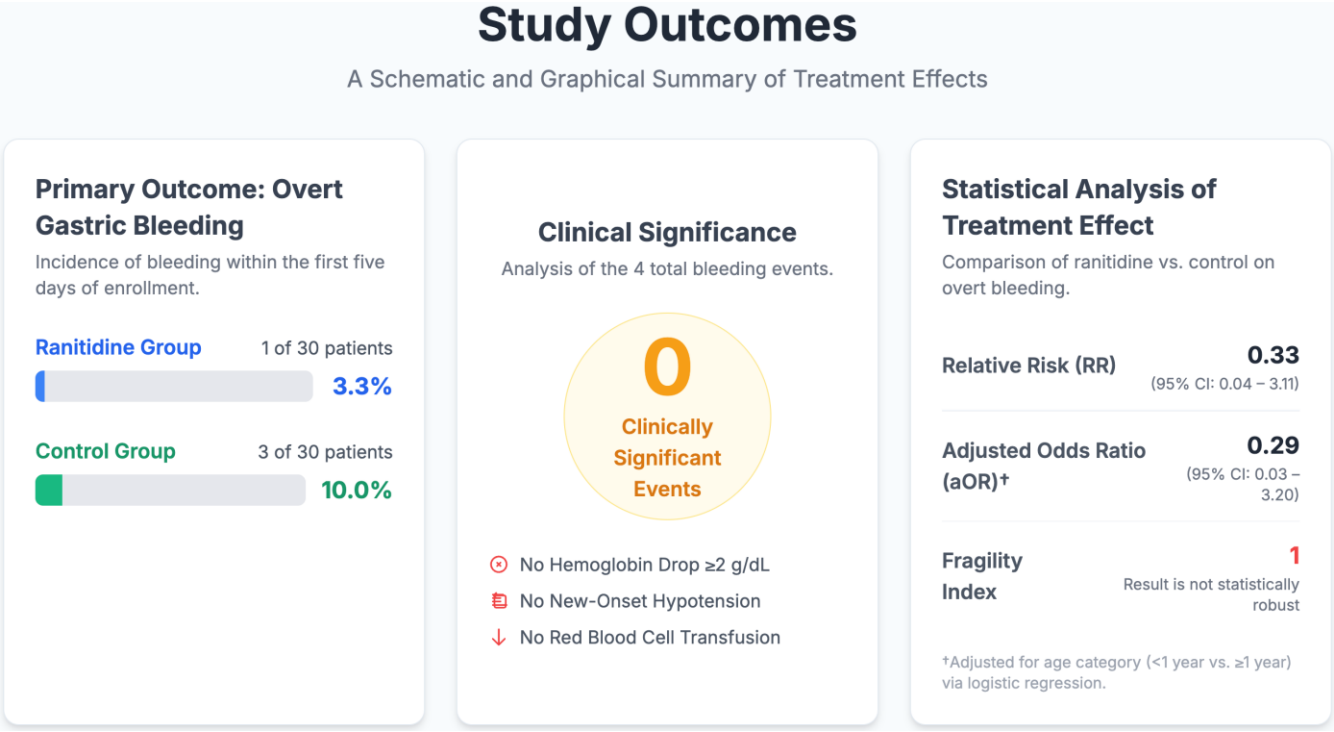

Figure 3. Study outcome.

4. Discussion

In this single-center, randomized controlled trial, the prophylactic administration of intravenous ranitidine was not associated with a statistically significant reduction in the incidence of overt gastric bleeding among a cohort of critically ill children.[11] While a threefold lower rate of bleeding was observed in the treatment arm—a numerical trend that might suggest a potential for clinical efficacy—this finding was not statistically robust. This conclusion of neutrality is further underscored by a Fragility Index of 1, indicating that the result is highly sensitive to even a single change in outcome events. The interpretation of this null finding is not straightforward and requires a cautious and multifaceted discussion. A null result in a clinical trial does not necessarily prove the absence of a treatment effect.[12] Instead, it can arise from several distinct and plausible explanations which must be explored in depth: (1) a true lack of efficacy in a genuinely low-risk population where there is little pathology to modify; (2) the inherent pharmacological limitations of ranitidine as a therapeutic agent, combined with the play of random chance; or (3) a conclusion that is fundamentally unreliable due to significant methodological limitations of the study itself, most notably a profound lack of statistical power and the potential for systematic bias. A comprehensive discussion requires a deep dive into the interplay between the pathophysiology of the disease, the pharmacology of the drug, and the methodology of the trial.

The most prominent interpretation, and the one most consistent with the observed data, is that the study population had a baseline risk of bleeding that was too low for any prophylactic intervention to demonstrate a significant benefit. The development of SRMD is a direct consequence of the failure of the stomach's intricate mucosal defense system in the face of overwhelming physiological stress.[13] This defense is not a single entity, but a dynamic, multi-layered barrier. The first line of defense is the pre-epithelial mucus-bicarbonate layer, a gel-like coating that traps secreted bicarbonate ions, creating a pH-neutral microenvironment directly adjacent to the epithelial cells, protecting them from the highly acidic gastric lumen. The second line is the epithelial layer itself, composed of cells linked by tight junctions that prevent back-diffusion of acid, and which possess a remarkable capacity for rapid repair and restitution after minor injury.[14] The final, and arguably most critical, line of defense is the sub-epithelial system, which relies on a dense network of mucosal capillaries to provide a rich blood supply. This blood flow is essential for delivering oxygen and nutrients for cellular metabolism, supplying bicarbonate to buffer acid, and washing away any acid that has breached the epithelial barrier.[15] In severe critical illness, such as profound septic shock or multi-organ dysfunction, this entire defensive structure collapses. The massive catecholamine surge and systemic inflammatory response cause intense splanchnic vasoconstriction, drastically reducing mucosal blood flow. This ischemia is the central, initiating insult. It cripples the epithelial cells, preventing them from producing mucus and bicarbonate. It halts the energy-dependent process of cellular restitution, and it leads to the generation of reactive oxygen species that further damage cell membranes. The mucosal barrier becomes leaky and fragile, allowing luminal acid to penetrate deep into the tissue, causing erosions, ulcerations, and bleeding.[16]

However, the cohort in our study did not, for the most part, exhibit this degree of severe physiological derangement. As evidenced by the Phoenix Sepsis Scores, the majority of our patients were not in a state of severe shock or multi-organ failure. In these less severe states of critical illness, while splanchnic perfusion may be reduced, it is not obliterated. The mucosal defense system, while stressed, remains largely competent. This intrinsic physiological resilience was further bolstered by a key iatrogenic factor: the high rate of early enteral nutrition. Over 80% of our patients received enteral feeding within 48 hours. Enteral nutrition is arguably one of the most potent non-pharmacological strategies for preventing

SRMD.[16] Its mechanisms are multifaceted: it provides essential nutrients directly to the enterocytes, supporting their metabolic function and repair capacity; the physical presence of food stimulates the release of protective gut hormones and increases splanchnic blood flow; and the nutrients themselves act as a direct buffer, neutralizing gastric acid. Therefore, our study population was one in which the primary drivers of SRMD were attenuated (less severe illness) and the primary protective mechanisms were robust (largely intact physiology) and actively supported (high rates of enteral nutrition). In such a scenario, the baseline rate of bleeding is expected to be low, which is precisely what we observed (a 10% incidence of non-clinically significant bleeding in the control group). The therapeutic action of ranitidine is applied to a system that is not critically broken. The absolute risk reduction observed was a mere 6.7%, yielding a number needed to treat (NNT) of 15 to prevent a single episode of overt bleeding that, in our study, had no clinical consequence for the patient. This finding aligns perfectly with the current paradigm shift towards risk stratification, suggesting that for the majority of PICU patients who do not have major risk factors, the marginal benefit of routine SUP does not outweigh the costs and potential for adverse effects.[17]

An alternative explanation is that the null result is a reflection of the pharmacological limitations of ranitidine itself, and that the observed difference in event rates (1 vs. 3) represents nothing more than statistical noise. Ranitidine is a competitive antagonist at the histamine-2 (H2) receptor on the basolateral membrane of gastric parietal cells. The binding of histamine to this receptor is a key pathway for stimulating the H+/K+ ATPase (the "proton pump") to secrete acid. By blocking this receptor, ranitidine effectively reduces acid secretion. However, this mechanism is not absolute and has notable limitations. First, it only blocks one of the three major pathways for acid stimulation (the others being gastrin and acetylcholine). This means that even with effective H2 blockade, other pathways can still stimulate acid secretion, leading to incomplete acid suppression compared to PPIs, which block the final common pathway of the proton pump itself. Second, and perhaps more importantly for this study, is the well-documented phenomenon of tachyphylaxis. With continuous exposure to an H2-receptor antagonist, the body responds by upregulating the number of H2 receptors on the parietal cells. This cellular adaptation means that the same dose of ranitidine becomes progressively less effective over time. This tolerance develops rapidly, often within 48 to 72 hours of initiating therapy. In our study, which followed patients for five days, it is highly plausible that any beneficial effect of ranitidine on gastric pH was most potent on days 1 and 2, and significantly diminished by days 4 and 5. The study, therefore, may not have tested the effect of sustained acid suppression, but rather the effect of a transient period of moderate acid suppression. Third, we did not measure the physiological effect of the drug. The absence of gastric pH monitoring means we cannot be certain that the administered dose of 1 mg/kg every 12 hours was sufficient to consistently achieve the therapeutic goal of maintaining a gastric pH above 4. The pharmacokinetics of ranitidine can be variable in critically ill children, and without direct measurement, we cannot rule out the possibility that the intervention was, for some or all of the patients, physiologically inadequate.[18] It is therefore possible that the study did not truly test the hypothesis of acid suppression, but rather the administration of a specific dose of ranitidine that may have had a variable and waning physiological effect.

Finally, the most critical and humbling interpretation is that the study's conclusions are unreliable due to its own profound methodological weaknesses. The scientific integrity of a trial rests on its ability to minimize bias and have sufficient statistical power to answer its research question. Our study was deficient in these areas. First and foremost, the study was severely underpowered. Our post-hoc analysis revealed a power of only 16%. This means that even if ranitidine had a true, clinically important benefit (such as a 50% reduction in bleeding), our

study had only a 16% chance of detecting it as statistically significant. There was an 84% chance of committing a Type II error—falsely concluding there is no effect when one truly exists. Therefore, the most statistically sound conclusion from our trial is not that there is "no difference," but that the study was incapable of reliably answering the question it set out to ask. Second, the open-label design introduces a significant and unquantifiable risk of bias. The lack of blinding of clinicians and research staff could have led to detection bias, where clinicians may have, consciously or unconsciously, scrutinized the nasogastric aspirates of control patients more frequently or interpreted ambiguous findings as positive, thus artifactually inflating the event rate in the control arm.[19] It could also have led to performance bias, where clinicians, knowing a patient was not receiving prophylaxis, may have been more aggressive with other protective measures like enteral feeding, thus biasing the results toward the null by making the control group healthier. Third, the choice of primary outcome—overt bleeding—proved to be a surrogate endpoint with no clinical relevance in this cohort. Our data show that none of the bleeding events were clinically significant. This suggests that the study was measuring a laboratory finding ("a coffee ground aspirate") rather than a patient-centered, clinically meaningful event ("hemorrhagic shock"). It is entirely possible that ranitidine is effective at preventing these minor, inconsequential bleeding episodes but has no effect on major, life-threatening hemorrhage. A study focused on a more clinically relevant endpoint is required.[20]

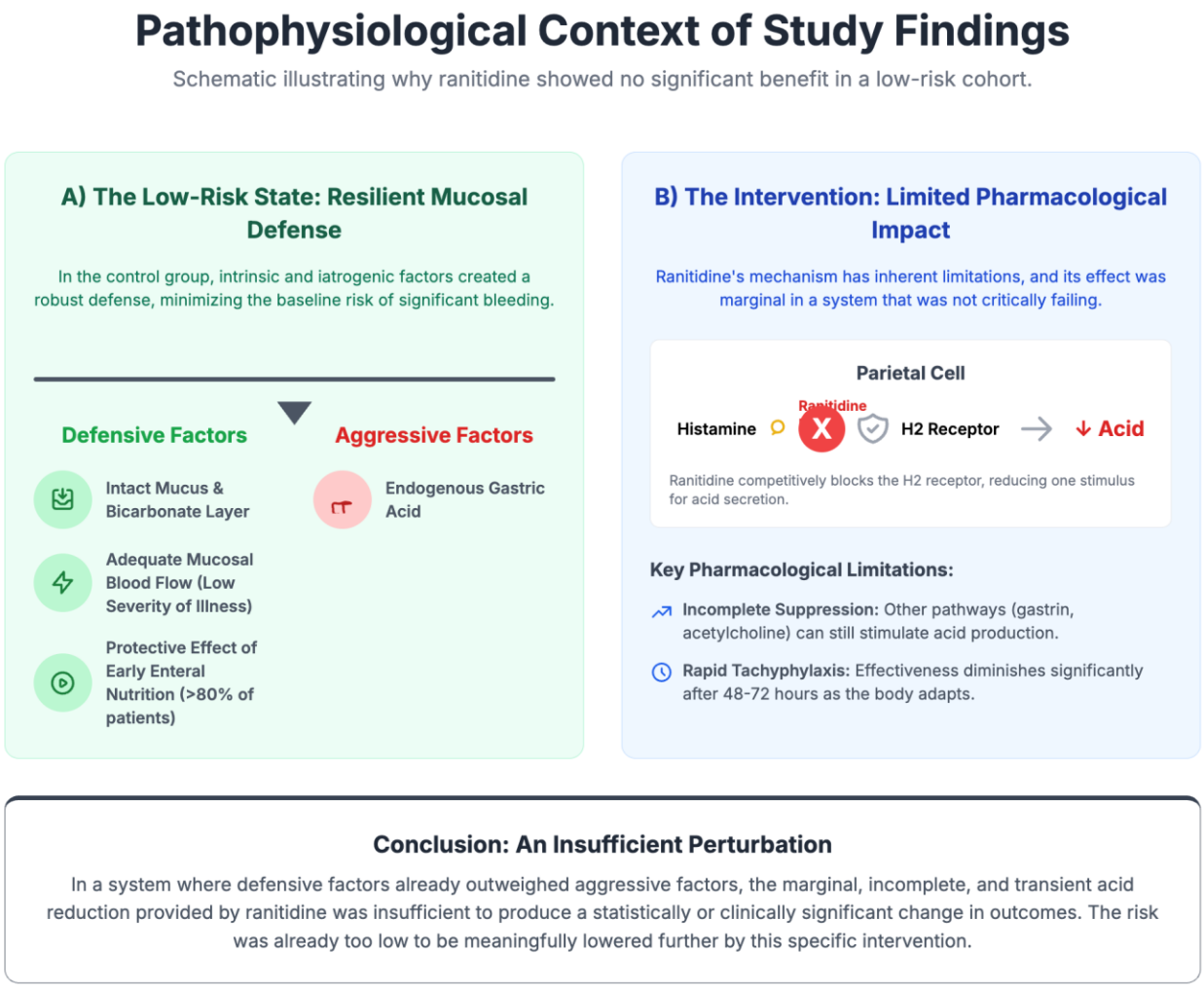

Figure 4. Pathophysiological of study findings.

Figure 4 provides a compelling physiological narrative that explains the study's primary finding: the lack of a statistically significant benefit from ranitidine. The schematic proposes that the neutral outcome was not necessarily a failure of the drug itself, but rather a consequence of applying a limited intervention to a patient population that was already at a very low risk for the outcome of interest. The investigation's cohort possessed a remarkably resilient gastric mucosal defense system, creating a physiological state where protective factors already held a significant advantage over aggressive factors. As illustrated in the diagram, this robust defense was multi-faceted. It included an intact mucus and bicarbonate layer, which acts as a primary chemical shield against stomach acid. This was further supported by adequate mucosal blood flow, a condition maintained because the majority of patients had a low severity of illness. Crucially, this intrinsic resilience was powerfully augmented by a key clinical intervention: the widespread use of early enteral nutrition, which was administered to over 80% of the patients. Enteral feeding is known to be highly protective, as it provides nutrients to gut cells, stimulates blood flow, and directly buffers acid. In this environment, the sole aggressive factor of endogenous gastric acid was effectively held in check, establishing a low-risk state where the likelihood of developing significant stress-related bleeding was minimal from the outset. The figure then contextualizes the pharmacological action of ranitidine within this low-risk system. The drug functions by competitively blocking the histamine-2 (H2) receptor on the stomach's parietal cells. This action curtails one of the primary signals for acid secretion, thereby reducing the overall acidity of the stomach. However, the diagram highlights two critical pharmacodynamic limitations that temper this effect. First, the acid suppression is incomplete; other signaling pathways involving gastrin and acetylcholine are unaffected by ranitidine and can continue to stimulate the parietal cells to produce acid. Second, the drug's effectiveness is transient due to the phenomenon of rapid tachyphylaxis. The body quickly adapts to the H2 receptor blockade, often within 48 to 72 hours, diminishing the drug's acid-suppressing capability over the course of the five-day study period. Figure 4 synthesizes these two concepts to arrive at its conclusion: the trial tested an insufficient perturbation on a highly stable system. The marginal, incomplete, and waning acid reduction provided by ranitidine was simply not powerful enough to produce a clinically or statistically meaningful change in a cohort whose risk was already negligible. The system's strong defensive posture meant there was no significant pathological process for the drug to modify. Therefore, the study's outcome is framed not as evidence against acid suppression in general, but as a clear illustration that its benefits are likely confined to high-risk patients, a group not represented in this trial.

For the sake of scientific transparency, the major limitations of this study must be explicitly summarized. The conclusions drawn should be interpreted with extreme caution in light of these weaknesses. The primary limitation is the lack of an a priori sample size calculation and the severely underpowered nature of the trial. This fundamentally limits the certainty of our null conclusion and makes it hypothesis-generating at best. The unblinded nature of the trial is a major source of potential detection and performance bias, which could have influenced the results in an unpredictable direction.[19] The study was conducted in a single PICU in Indonesia. The patient population, case mix, and standard care protocols may not be generalizable to other centers, either nationally or internationally. The primary outcome was not clinically significant bleeding. The reliance on a surrogate endpoint that proved to be of no clinical consequence to the patients limits the clinical applicability of the findings. We used the Phoenix Sepsis Score to characterize illness severity. While this is the latest international consensus tool for pediatric organ dysfunction, it has not been validated as a risk-stratification tool for SRMD. Proposing it as a clinical decision tool for SUP

based on our findings would be a critical and unsupported leap of logic. Its use here is descriptive and exploratory only. The absence of gastric pH monitoring means we cannot confirm that the intended physiological effect of the intervention was achieved, weakening the link between the intervention and the outcome. Despite its significant limitations, this study serves an important purpose. It provides randomized trial data that, while not definitive, aligns with the growing international consensus against the routine, indiscriminate use of SUP in lower-risk children. The primary clinical implication is that clinicians should prioritize a formal assessment of established SRMD risk factors—namely mechanical ventilation and coagulopathy—before reflexively prescribing acid-suppressive therapy.[20] Our data suggest that in a population where these major risk factors are largely absent, a strategy of withholding prophylaxis is likely to be safe. The clear message for the research community is the urgent need for a large, multicenter, adequately powered, and placebo-controlled randomized trial to definitively answer this question. Future studies must be powered to detect a difference in a patient-centered outcome, such as clinically significant bleeding, and should be conducted across diverse global settings to ensure generalizability. Such a trial would be essential to finally establish an evidence-based, universally accepted threshold for initiating and withholding stress ulcer prophylaxis in critically ill children.

5. Conclusion

In this small, single-center, underpowered randomized controlled trial, the routine prophylactic use of intravenous ranitidine did not result in a statistically significant reduction in the incidence of overt gastric bleeding in a population of critically ill children who were found to have a low baseline risk of this complication. The interpretation of this neutral finding is complex and is severely limited by significant methodological weaknesses, including a high risk of bias and a profound lack of statistical power. The study does not support the routine use of ranitidine for stress ulcer prophylaxis in similar low-risk pediatric populations. The findings, while not definitive, underscore the critical importance of risk stratification in clinical decision-making and highlight the urgent need for large, methodologically rigorous trials to provide definitive guidance on this common clinical practice.

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